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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,358	HOLDER ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-26,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 8-26 and 30-31 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 2/13/2006 in response to the previous Office Action (10/25/2005) is acknowledged. Rejections of claims 1-29 under 35 U.S.C. § 112, second paragraph (item 6), the Double Patenting rejection under 35 U.S.C. 101 and the prior art rejection (item 4) have been obviated. Even though applicants overcome most of the rejections by the amendment, the amendment also raise new issues that need further rejection. The enablement rejection (item 5) has been maintained.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claim 8 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/715,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is significant overlap between the instant claims 1-8 and claim 8 of copending Application No. 10/715,556. Note that most of the species recited in claim 8 are present in claim 8 of the copending Application No. 10/715,556.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-15, 17-26 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The new proviso recited in claims 9 and 17 i.e. "(2) the compound is not 3-{4-(3,4,5-trimethoxyaniinocarbonyl)-3-oxo-2,3-dihydropyridazine.....(3) when A is NHCOCH(CH3)2, Ar is not unsubstituted or at least monosubstituted bicyclic heteroaryl" is lacks description. Even a negative limitation requires description, *Ex Parte Grasselli,* 231 USPQ 393.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of cranial and spinal traumas and peripheral neuropathies, obesity, type II diabetes, atherosclerotic cardiovascular diseases, essential hypertension, polycystic ovary syndrome, does not reasonably provide enablement for the treatment of neurodegenerative diseases, strokes, metabolic diseases, syndrome X and immunodeficiency and a method of inhibiting GSK-3β or the

phosphorylation of the Tau protein in a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is recited for example in claim 17 a method of treating neurodegenerative diseases, strokes, metabolic diseases, syndrome X and immunodeficiency and a method of inhibiting GSK-3β or the phosphorylation of the Tau protein in a patient, but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims:

(A) - The scope of use that applicants intend to claim is very broad.

Metabolic diseases

Disorders may affect metabolism, which is how the body processes substances needed to carry out its functions. Such disorders are often caused by genetic abnormalities that

result in the absence of a specific enzyme needed to stimulate a metabolic process. Depending on the disorder, the effects may be serious or fairly harmless.

There are several types of metabolic disorders: Carbohydrate Metabolism Disorders, Pyruvate Metabolism Disorders, Aminoacid Metabolism Disorders, etc.

Carbohydrate Metabolism Disorders

Carbohydrates are sugars. Many sugars besides the well-known glucose, sucrose, and fructose are present in foods. Some sugars, such as sucrose, must be processed (metabolized) by enzymes in the body before they can be used as a source of energy. If the enzymes needed to process them are missing, these sugars can accumulate, causing problems. Two examples are:

Galactosemia (a high blood level of galactose) is usually caused by the lack of galactose 1-phosphate uridyl transferase, one of the enzymes necessary for metabolizing galactose. This disorder is present from birth.

Hereditary fructose intolerance is a hereditary disorder in which the body cannot use fructose because the enzyme phosphofructaldolase is absent. As a result, fructose 1-phosphate, a by-product of fructose, accumulates in the body, blocking the formation of glycogen and its conversion to glucose for use as energy.

Pyruvate Metabolism Disorders

Pyruvate is formed in the processing of carbohydrates, fats, and proteins. Hereditary problems with the processing of pyruvate can cause a wide variety of disturbances.

Pyruvate is an energy source for mitochondria, the energy-generating components of a cell. A problem with pyruvate metabolism can disturb the functioning of the mitochondria, causing any of a variety of symptoms, such as muscle damage, mental retardation, seizures, a buildup of lactic acid leading to excess acid in the body (acidosis), or failure of organ function, including that of the heart, lungs, kidneys, or liver. Such problems may develop any time between early infancy and late adulthood. Exercise, infections, or alcohol consumption can worsen symptoms, leading to severe lactic acidosis with muscle cramping and weakness. Two examples are:

A deficiency of the pyruvate dehydrogenase complex, a group of enzymes needed to process pyruvate, results in insufficient levels of acetyl coenzyme A, which is essential for energy production. The major symptoms include slowed muscle action, poor coordination, and a severe balance problem that makes walking nearly impossible. In addition, seizures, mental retardation, and brain malformation may occur. This disorder cannot be cured, but some people are helped by a diet high in fat.

Absence of pyruvate carboxylase, an enzyme, interferes with or blocks the production of glucose in the body. Lactic acid and ketones build up in the blood, causing nausea and vomiting. Often this disease is fatal. The synthesis of amino acids, the building blocks of proteins, also depends on pyruvate carboxylase. When this enzyme is missing, the production of neurotransmitters (substances that transmit nerve impulses)

is reduced, leading to a variety of neurologic symptoms, including severe mental retardation. Low blood sugar levels (hypoglycemia) and the buildup of acids in the blood (acidosis) may be relieved by eating frequent carbohydrate-rich meals, but no replacements for the missing neurotransmitters are available to treat the neurologic symptoms.

Amino Acid Metabolism Disorders

Amino acids, the building blocks of proteins, have many functions in the body. Hereditary disorders of amino acid processing can be defects in either the breakdown of amino acids or their transport into cells. Many of these disorders, including phenylketonuria, have been identified.

Phenylketonuria *(PKU, phenylalaninemia, phenylpyruvic oligophrenia)* is a hereditary disorder in which the enzyme that processes the amino acid phenylalanine is missing, resulting in a dangerously high level of phenylalanine in the blood. Phenylalanine is normally converted to tyrosine, another amino acid, and eliminated from the body. Without the enzyme that converts it, phenylalanine builds up in the blood and is toxic to the brain, causing mental retardation.

There are other metabolic disorders, which affect e.g. calcium and phosphorus as well as other elements in the body.

Neurodegenerative diseases

It has been recited in claims 17-25, a method of treating neurodegenerative diseases. Neurodegenerative disorders are extremely varied in origin and nature of effect. The origin and the nature of many neurodegenerative disorders such as Huntington's disease, Pick's disease, Frontotemporal dementia, Cerebro-Oculo-Facio-Skeletal (COFS) syndrome (cranofacial and skeletal abnormalities), Motor neuron disease (muscle weakness), Corticobasal ganglionic degeneration, Creutzfeldt-Jacob disease (fatal disease), Dementia with Lewy bodies, and Progressive supranuclear palsy Dementia are different one from the other. Many neurodegenerative disorders are untreatable to this day.

The symptoms and nature of these diseases are also different one from the other. It can be shown that many of these neurodegenerative disorders have different origin and nature of effect. Some neurodegenerative disorders are hereditary (Charcot-Marie-Tooth disease). Many neurodegenerative disorders vary in how they affect the body and its functions. Diseases such as Cerebral palsy, and Parkinson's disease affect the movement of the patient. Diseases such as Alzheimer's disease affect the memory of the patient.

Stroke

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech

disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Immunodeficiency

Immunodeficiency (or immune deficiency) is a condition resulting from a defective immunological mechanism; may be primary (due to a defect in the immune mechanism per se) or secondary (dependent upon another disease process), specific (due to defect in either the B-lymphocyte or T-lymphocyte system, or both) or nonspecific (due to defect in one or another component of the nonspecific immune mechanism). The treatment of "immunodeficiency" generally would be an unprecedented feat. For a compound or genus to be effective against "immunodeficiency" generally is contrary to medical science. The "immunodeficiency" are processes which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes.

Five classes of primary immunodeficiency diseases have been identified:

1. T-lymphocyte disorders (such as the DiGeorge anomaly and chronic mucocutaneous candidiasis);

2. B-lymphocyte disorders (such as X-linked agammaglobulinemia, common variable immunodeficiency, and selective immunoglobulin A deficiency);

3. Combined T- and B-lymphocyte disorders (such as severe combined immunodeficiency, i.e. SCID, the Wiskott-Aldrich syndrome and ataxia telangiectasia);

4. Phagocytic disorders (such as chronic granulomatous disease) and

5. Complement disorders (such as C2 deficiency and C3 deficiency).

Although the exact etiology of many immunodeficiency diseases is unknown, several etiologic factors have been identified in specific disorders. When normal maturation of the immune system is impaired as in an enzyme or hormone deficiency, immunodeficiency can result. Many immunodeficiency diseases are genetically determined. In some forms of agammaglobulinemia and SCID, an X-linked recessive pattern of inheritance has been demonstrated. In other immunodeficiency diseases, an autosomal recessive pattern of inheritance is evident.

Some immune deficiencies result from environmental factors or occur secondary to other causes. One example is the Acquired Immune Deficiency Syndrome, also known as AIDS, which is caused by the HIV virus. Other immune deficiency diseases occur or are acquired as the result of having cancer, severe nutritional disorders, burns, infections, exposure to radiation or organ transplantation.

Syndrome X

It has been recited a method of treating Syndrome X, but the specification is not enabled for such a scope. Syndrome X is a cluster of risk factors that together, put someone at higher risk of coronary artery disease. These risk factors include: central obesity (excessive fat tissue in the abdominal region), glucose intolerance, high triglycerides and low HDL cholesterol, and high blood pressure.

(B). Scope of Compounds - The scope of the compounds is broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of A1, A2, and Ar.

(2). Direction of Guidance: The amount of direction or guidance is minimal. The dosage range is 300 fold and hence largely useless. The dosage is completely generic, it is the same regardless of which disorder is being treated.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these pyridazine derivative compounds are in use for the treatment of metabolic disorder.

(4). Working Examples: There is no any working example that indicates the inhibition of GSK-3β, which in return is presumed to treat neurodegenerative diseases, strokes,

metabolic diseases, syndrome X or immunodeficiency. There is no data for any actual treatment of disease or of any animal model for treatment of disease.

(5). Nature of the Invention and Predictability: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(6). The Relative Skill of Those in the Art: The skill level in this art is too low, because no compound effective against neurodegenerative diseases, strokes, metabolic diseases, syndrome X or immunodeficiency has ever been found.

In terms of the individual metabolic disorders, this is completely varied. It ranges from areas where the skill level is high, as in carbohydrate metabolic disorders, to a deficiency of the pyruvate dehydrogenase complex, where the skill level is so low that there is no effective pharmacological treatment.

In regard to stroke, the skill level in this is so low. Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP,

and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well. Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining a neuroprotective treatment of stroke was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there is cited Chalmers (TiPS Vol 17, pages 166-172 April 1996), which states flatly on page 170 that, "At present, there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." For example, Pentoxifylline has been one of the most intensely studied, with dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide-

ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. Applicants' compounds have been subjected to far less study.

(7). The Quantity of Experimentation Necessary: Immense, especially in view of points (1) and (6).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

In regard to a method for inhibiting GSK-3β or the phosphorylation of the Tau protein in a patient, the claim covers the inhibition of GSK-3β or the phosphorylation of the Tau protein in any patient. This is not a proper claim language. It is recommended that applicants delete claims 9-16 to overcome part of the rejection or recite specific diseases i.e. applicants have to link a method of inhibition GSK-3β or the phosphorylation of the Tau protein with the treatment of specific diseases.

Response to arguments

Applicant's argument filed 2/13/2006 has been fully considered but it is not persuasive.

Applicants argue that they have showed anticancer potency as indicated by the IC_{50} values of inhibiting the phosphorylation of the Tau protein. The examiner disagrees with applicants. There is nothing in the disclosure that correlates the *in vitro* data to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (i.e. neurodegenerative diseases, stroke, metabolic diseases, syndrome X and immunodeficiency), some of which have been proven to be extremely difficult to treat. Please see above 1-7 for more details.

Claim Objections

8. Claims 17 and 24 are objected to because of the following informalities: the recitation of the term "strokes" is objected to because it is written in plural form. It should read as "stroke". Appropriate correction is required.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte whose telephone number is (571)-272-0667. The examiner can normally be reached on M-F (9.00- 5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

KH
March 21, 2006